SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

BENLAXID 6,9 g poeder voor drank

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of Benlaxid contains the following active substances:

Macrogol 3350	6.563 g
Sodium Chloride	0.1754 g
Sodium Hydrogen Carbonate	0.0893 g
Potassium Chloride	0.0233 g

The content of electrolyte ions per sachet when made up to 62.5 ml of solution is as follows:

Sodium	65	mmol/l
Chloride	53	mmol/l
Potassium	5.0	mmol/l
Bicarbonate	17	mmol/l

Excipients with known effect:
Each sachet contains 12.5 mg of Aspartame (E951).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution

Free flowing white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of chronic constipation in children 1 to 11 years of age.

For the treatment of faecal impaction in children from the age of 5 years, defined as refractory constipation with faecal loading of the rectum and/or colon.

4.2 Posology and method of administration

Posology

Chronic constipation

The usual starting dose is 1 sachet daily for children aged 1 to 6 years, and 2 sachets daily for children aged 7 – 11 years. The dose should be adjusted up or down as required

to produce regular soft stools. If the dose needs increasing this is best done every second day. For children below 2 years of age, the maximum recommended dose should not exceed 2 sachets a day. For children aged 2 to 11 years, the maximum recommended dose needed does not normally exceed 4 sachets a day

Treatment of children with chronic constipation needs to be for a prolonged period (at least 6 – 12 months). Treatment should be stopped gradually and resumed if constipation recurs.

Faecal impaction

A course of treatment for faecal impaction with Benlaxid is for up to 7 days as follows:

Daily dosage regimen:

	Number of Benlaxid sachets						
Age (years)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
5 - 11	4	6	8	10	12	12	12

The daily number of sachets should be taken in divided doses, all consumed within a 12 hour period. The above dosage regimen should be stopped once disimpaction has occurred. An indicator of disimpaction is the passage of a large volume of stools. After disimpaction it is recommended that the child follows an appropriate bowel management program to prevent reimpaction (dosing for prevention of re-impaction should be as for patients with chronic constipation; see above).

Benlaxid is not recommended for children below 5 years of age for the treatment of faecal impaction, or in children below 1 year of age for the treatment of chronic constipation. For patients of 12 years and older it is recommended to use *Benlaxid Adult* .

Patients with impaired cardiovascular function:

There are no clinical data for this group of patients. Therefore Benlaxid is not recommended for treating faecal impaction in children with impaired cardiovascular function.

Patients with renal insufficiency:

There are no clinical data for this group of patients. Therefore Benlaxid is not recommended for treating faecal impaction in children with impaired renal function.

Method of administration

Each sachet should be dissolved in 62.5 ml (quarter of a glass) of water. The correct

number of sachets may be reconstituted in advance and kept covered and refrigerated for up to 24 hours. For example, for use in faecal impaction, 12 sachets can be made up into 750 ml of water.

4.3 Contraindications

Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis and toxic megacolon.
Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

The fluid content of Benlaxid when re-constituted with water does not replace regular fluid intake and adequate fluid intake must be maintained.

Diagnosis of faecal impaction/faecal loading of the rectum should be confirmed by the physical or radiological examination of the abdomen and rectum.

Rarely symptoms indicating shifts of fluid/electrolytes e.g. oedema, shortness of breath, increasing fatigue, dehydration and cardiac failure have been reported in adults when using preparations containing macrogol. If this occurs Benlaxid should be stopped immediately, electrolytes measured, and any abnormality should be treated appropriately.

When used in high doses to treat faecal impaction this medicinal product should be administered with caution to patients with impaired gag reflex, reflux oesophagitis or diminished levels of consciousness.

Benlaxid solution when reconstituted has no calorific value.

The absorption of other medicinal products could transiently be reduced due to an increase in gastro-intestinal transit rate induced by Benlaxid (see section 4.5).

This medicinal product contains 93.4 mg sodium per sachet, equivalent to 4.6 % of the WHO recommended maximum daily intake for sodium.
The maximum daily dose of this product in patients with faecal impaction is equivalent to 55.4 % of the WHO recommended maximum daily intake for sodium.
The maximum daily dose of this product in patients with chronic constipation is equivalent to 18.4% of the WHO recommended maximum daily intake for sodium
Benlaxid is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicinal product contains 12.5 mg aspartame per sachet. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.
Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
This medicine contains 5.0 mmol potassium per sachet. To be taken into consideration by

patients with reduced kidney function or patients on a controlled potassium diet.

In patients with swallowing problems, who need the addition of a thickener to solutions to enhance an appropriate intake, interactions should be considered, see section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products in solid dose form taken within one hour of administration of large volumes of macrogol preparations (as used when treating faecal impaction) may be flushed from the gastrointestinal tract and not absorbed.

Macrogol raises the solubility of medicinal products that are soluble in alcohol and relatively insoluble in water.

There is a possibility that the absorption of other medicinal products could be transiently reduced during use with Benlaxid (see section 4.4). There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics.

Benlaxid may result in a potential interactive effect if used with starch-based food thickeners. Macrogol ingredient counteracts the thickening effect of starch, effectively liquefying preparations that need to remain thick for people with swallowing problems.
It is recommended to wait at least 2 hours between the intake of Benlaxid and other medicinal product.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of Benlaxid in pregnant women. Studies in animals have shown indirect reproductive toxicity (see section 5.3). Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible.

Benlaxid can be used during pregnancy.

Breastfeeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Macrogol 3350 is negligible.
Benlaxid can be used during breast-feeding.

Fertility

There are no data on the effects of on fertility in humans. There were no effects on fertility in studies in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Benlaxid has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Reactions related to the gastrointestinal tract occur most commonly.
These reactions may occur as a consequence of expansion of the contents of the

gastrointestinal tract, and an increase in motility due to the pharmacologic effects of Benlaxid .
In the treatment of chronic constipation, diarrhoea or loose stools normally respond to a reduction in dose.
Diarrhoea, abdominal distension, anorectal discomfort and mild vomiting are more often observed during the treatment for faecal impaction. Vomiting may be resolved if the dose is reduced or delayed.

The frequency of the adverse reactions listed below is defined using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1000); and very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	***Adverse event***
Immune system disorders	Rare	Allergic reactions including anaphylactic reaction.
	Not known	Dyspnoea and skin reaction (see below)
Skin and subcutaneous tissue disorders	Not Known	Allergic skin reactions including angioedema, urticaria, pruritus, rash, erythema
Metabolism and nutrition disorders	Not known	Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia.
Nervous system disorders	Not known	Headache.
Gastrointestinal disorders	Very common	Abdominal pain, borborygmi.
	Common	Diarrhoea, vomiting, nausea and anorectal discomfort.
	Uncommon	Abdominal distension, flatulence.
	Not known	Dyspepsia and peri-anal inflammation.
General disorders and administration site conditions	Not known	Peripheral oedema.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

Severe abdominal pain or distension can be treated by nasogastric aspiration. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxatives.
ATC code: A06A D65
Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defaecation. Electrolytes combined with macrogol 3350 are exchanged across the intestinal barrier (mucosa) with serum electrolytes and excreted in faecal water without net gain or loss of sodium, potassium and water.

In an open study of Benlaxid in chronic constipation, weekly defaecation frequency was increased from 1.3 at baseline to 6.7, 7.2 and 7.1 at weeks 2, 4 and 12 respectively. In a study comparing Movicol and lactulose as maintenance therapy after disimpaction, weekly stool frequency at the last visit was 9.4 (SD 4.46) in the Benlaxid group compared with 5.9 (SD 4.29). In the lactulose group 7 children re- impacted (23%) compared with no children in the Benlaxid group.

In one retrospective-prospective study, 35 patients <24 months' age were treated with Benlaxid for functional constipation for a mean duration of 4.6 ± 3.67 months (from 3 weeks to 18 months). Mean stool frequency before treatment was 2.34 ± 0.98 per week. Following treatment, the frequency of bowel movements was 7.31 ± 1.60 per week, which was a significant difference from baseline ($p < 0.001$). There was also a significant difference in improvement from baseline in the stool consistency score after treatment (1.57 ± 0.54 vs. 3.34 ± 0.58; $p < 0.001$).

In an observational, prospective, longitudinal, parallel group study 62 children aged 1-17 years were treated for chronic constipation with Macrogol / Benlaxid for 12 weeks. Of these 62 patients 30 were aged 1 - 3 years. The number of bowel movements per week was similar in both groups at weeks 6 and 12: mean (SD) 6.1 (2.5) and 6.0 (2.7) at 6 weeks, and 4.6 (2.2) and 5.4 (1.8) at 12 weeks for Macrogol and Benlaxid. Similar improved efficacy results were observed in 2 further trials where patients 6 months – 15 years were treated with Macrogol plus electrolytes.

For the indication of faecal impaction comparative studies have not been performed with other treatments (e.g. enemas). In a non-comparative study in 63 children, *Benlaxid +Electrolytes* (Pediatric) cleared the faecal impaction in the majority of patients within 3-7 days of treatment. For the 5 - 11 years age group the average total number of sachets of Benlaxid required was 47.2.

5.2 Pharmacokinetic properties

Macrogol 3350 is metabolised along the gastro-intestinal tract. It is virtually unabsorbed from the gastrointestinal tract due to its heavy molecular weight. Any macrogol 3350 that

is absorbed (≤ 0,1%) is excreted via the urine.

5.3 Preclinical safety data

Preclinical studies provide evidence that macrogol 3350 has no significant systemic toxicity potential, based on conventional studies of pharmacology, repeated dose toxicity and genotoxicity.

There were no direct embryotoxic or teratogenic effects in rats even at maternally toxic levels that are a multiple of 66 x the maximum recommended dose in humans for chronic constipation and 25 x for faecal impaction. Indirect embryofetal effects, including reduction in fetal and placental weights, reduced fetal viability, increased limb and paw hyperflexion and abortions, were noted in the rabbit at a maternally toxic dose that was 3.3 x the maximum recommended dose in humans for treatment of chronic constipation and 1.3 x for faecal impaction. Rabbits are a sensitive animal test species to the effects of GI-acting substances and the studies were conducted under exaggerated conditions with high dose volumes administered, which are not
clinically relevant. The findings may have been a consequence of an indirect effect of Benlaxid related to poor maternal condition as the result of an exaggerated pharmacodynamic response in the rabbit. There was no indication of a teratogenic effect.

There are long-term animal toxicity and carcinogenicity studies involving macrogol 3350. Results from these and other toxicity studies using high levels of orally administered high molecular weight macrogols provide evidence of safety at the
recommended therapeutic dose

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Orange Flavour
- Maltodextrin (maize),
- Arabic gum (E414),
- Citric acid (E330),
- Butylated hydroxyanisole (E320)
- Other flavouring substances

Lemon Flavour
- Maize maltodextrin,
- Flavouring preparations,
- Flavouring substances,
- Natural flavouring substances,
- Alpha-tocophero(E307)

Aspartame (E951)
Sucralose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.
Reconstituted solution: 24 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Reconstituted solution: Store in a refrigerator (2ºC – 8ºC) or at room temperature (19ºC-25ºC)

6.5 Nature and contents of container

Sachet: laminate consisting of four layers: low density polyethylene (LDPE), aluminium, LDPE and paper

Pack sizes: boxes of 20 or 30 sachets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused solution should be discarded within 24 hours.

7 MARKETING AUTHORISATION HOLDER

Italfarmaco, S.A.
Calle San Rafael 3
28108 Alcobendas, Madrid
Spanje

8 MARKETING AUTHORISATION NUMBER(S)

RVG 128690

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 18 oktober 2022

10 DATE OF REVISION OF THE TEXT